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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,431	01/22/2001	James Arthur Hoffmann	X-12383M	5086

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,431	HOFFMANN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *161-163* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *161-163* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 14 July 2004 has been entered.

Status of Application, Amendments and/or Claims

The amendment filed 14 July 2004 has been entered in full. Claims 159-160 were cancelled. New claims 161-163 were added. Claims 161-163 are under examination.

The declarations of Michael R. DeFelippis, Leo Plouffe Jr. and John M. Beals, filed with the amendment and response under 37 CFR 1.132 have been received and entered into the record.

Information Disclosure Statement

The information disclosure statement (IDS) submitted 14 July 2004 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits. However, some of references cited therein are not true publications with a

publication date, they are not fully in compliance with 37 CFR 1.97 and thus they will not be printed on the face of the patent issuing from this application.

Withdrawn Objections And/Or Rejections

The provisional rejection of claims 159 and 160 under the judicially created doctrine of double patenting over claim 128 of copending Application No. 09/928,198 in view of Keene *et al.*, The Journal of Biological Chemistry Vol. 264/9: 4769-4775 (1989), Skrabanja *et al.,* EP 0853 945 A1 and Andya *et al.*, US Patent No. 6,267,958 B1 as set forth at pages 7-9 of the previous Office Action (11 March 2004) is *withdrawn* in view of the amendment (14 July 2004).

Claim Rejections - 35 USC § 103

New claims 161 and 162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keene *et al.*, The Journal of Biological Chemistry Vol. 264/9: 4769-4775 (1989) (reference of record) in view of Skrabanja *et al.*, EP 0853 945 A1 (cited in Applicant's IDS) and Andya *et al.*, US Patent No. 6,267,958 B1 (reference of record).

The instant claims are drawn to a pharmaceutically acceptable solution formulation comprising human FSH (concentrations 5.0ug/ml to 2mg/ml) and a preservative in a aqueous diluent, wherein the preservative is selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol and mixtures thereof, wherein the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6,

held together by noncovalent interactions and wherein the formulation is suitable for multi-dose administration by injection.

Keene *et al.* teach the expression of biologically active recombinant human FSH (abstract, page 4769, 3rd paragraph; page 4771, 3rd paragraph and 6th paragraph). Human FSH α-subunit is SEQ ID NO:5 (1-92 amino acids). Human FSH β-subunit is SEQ ID NO:6 (1-111 amino acids). Keene *et al.* describe the construction and expression of human FSH α and β-subunits (page 4770, first paragraph). Recombinant FSH protein inherently meets the limitation "held together by noncovalent interactions". Keene *et al.* teach the biological activity of recombinant human FSH (page 4772, 2nd paragraph-page 4773 and Figures 6, 7). Keene *et al.* do not disclose pharmaceutical formulations of recombinantly expressed human FSH comprising preservatives, wherein the formulation is suitable for multi-dose administration.

Skrabanja *et al.* teach a stable formulation comprising liquid FSH (abstract; page 3, lines 15-18, 35-38 and page 4, lines 11-13). Liquid FSH comprises all forms including human recombinant FSH (page 3, lines 35-54). Skrabanja *et al.* teach concentrations of FSH which overlap the concentrations in the instant claims (page 5, lines 5-14). Skrabanja *et al.* teach an article of manufacture comprising a vial or a pen-injector device. The formulation can be in the form of a cartridge for multiple uses (page 5, lines 21-45).

Andya *et al.* teach stable lyophilized protein formulations, which when reconstituted generate a stable multi-use formulation (column 1, lines 52-column 2, line 9). The reconstituted formulation may be used as a multi-use formulation (column 2,

lines 20-30). Andya *et al.* teach the follicle-stimulating hormone (FSH) as a suitable protein in the formulation (column 6, lines 44-50). Andya *et al.* teach that a preservative can be added to the diluent to reduce bacterial action in the reconstituted formulation, thus facilitating the production of a multi-use reconstituted formulation. Examples of preservatives include m-cresol (column 9, lines 46-58).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Keene, Skrabanja and Andya to make the instant invention of a pharmaceutical acceptable solution formulation suitable for multi-use comprising human FSH and m-cresol. The motivation and expected success is provided by Keene, Skrabanja and Andya. The expression of biologically active recombinant human FSH (Keene *et al.*) avoids the need of purifying FSH from natural sources. The cartridge of Skrabanja *et al.* provides the convenience of stable multiple uses of FSH pharmaceutical formulations. Andya *et al.* teach that formulations comprising FSH, which have preservatives such as m-cresol reduce bacterial action.

Applicant's arguments submitted in the response received 14 July 2004 have been fully considered but are not found to be persuasive for the following reasons. The Michael R. DeFelippis, Leo Plouffe, Jr. and John M. Beals declarations under 37 CFR 1.132 filed 14 July 2004 are insufficient to overcome the rejection of claims 161-162 based upon 35 U.S.C. 103(a) for the following reasons.

Applicant cites Donaldson *et al.,* U.S. Patent No. 5,162,306. Applicant states that Donaldson conveys to the person of skill in the art that preservatives, other than thymol, damage FSH and cause instability of the product. Applicant argues that the prior

art cited by the Examiner, when combined does not make the invention obvious. Applicant states that Keene merely provides the sequence of human FSH, and was cited by the Examiner for that purpose alone. Skrabanja provides a liquid FSH formulation, in the same concentration range as the instant application, but preservatives are not taught. The examples of Skrabanja demonstrate the stability of unpreserved formulations in cartridges for multiple uses. Applicant states that Andya provides lyophilized formulations that can be reconstituted to yield high concentration liquid formulations and then exemplified only two proteins in a list more than 100. Applicant argues that Andya requires a concentration greater than or equal to 50mg protein/mL diluent. Applicant contends that Andya does not teach or suggest that a lower concentration protein formulation would be stable and a person of skill in the art would not expect that every protein on the list would yield a stable formulation if a preservative were added. Applicant asserts that to arrive at the instant invention, the Examiner must specifically select FSH from the general and extensive list of proteins in Andya, select the appropriate preservatives from another list of optional ingredients, disregard the high concentration of Andya and instead use the lower concentration in Skrabanja.

Applicant's arguments have been fully considered but are not deemed persuasive. Firstly, the line of argument regarding whether the Andya Patent provides an enabling disclosure will not be discussed because an Examiner cannot comment on the prosecution of an issued patent. The disclosure and claims of an issued patent are presumed to be fully enabled. Secondly, Donaldson *et al. (published November 1992)*

may teach that preservatives, other than thymol, damage FSH and cause instability of the product, but Andya *et al. (published July 2001)* teach otherwise. The fact that Andya does not disclose lower FSH concentrations is moot because the Skrabanja reference teaches FSH formulations in the same concentration range as the instant claims. Contrary to Applicant's assertion, the 103(a) is based on the combination of all three references.

Finally, Applicant refers to the DeFelippis, Plouffe and Beals declarations which assert the instability of FSH, the long felt need to improve FSH formulations and the unpredictability of protein-preservative compatibility. Applicant submits that adoption by others (FDA approval of FSH formulations containing m-cresol) is further evidence of the nonobviousness of this product. This has been fully considered but is not found to be sufficient to withdrawn the rejection because Anyda *et al.* teach formulations comprising FSH and m-cresol. Thus the arguments regarding instability, protein-preservative compatibility and long felt need are not convincing. There can be no long felt need in the face of the literature suggesting the claimed invention. Furthermore, the requirement for non-obviousness of the claimed invention is different from the FDA standard for drug approval. FDA approval is not a prerequisite for finding a formulation nonobvious within the meaning of the patent laws.

Therefore, the scientific reasoning and evidence as a whole indicates that the rejection under 35 U.S.C. 103(a) should be maintained.

New claims 161 and 163 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keene *et al.*, The Journal of Biological Chemistry Vol. 264/9: 4769-4775 (1989) (reference of record) in view of Skrabanja *et al.*, EP 0853 945 A1 (cited in Applicant's IDS) and L'Italien *et al.* US Patent No. 6,136,784 (reference of record).

The teachings of Keene *et al.* and Skrabanja *et al.* are described above. None of the references teach the use of phenol.

L'Italien *et al.* teach formulations of amylin agonist peptides in an aqueous system (column 18, lines 25-28 and lines 38-41). L'Italien *et al.* state that the use of antimicrobial preservatives such as phenol is present in the formulation of product design to allow the patient to withdraw multiple doses (column 18, lines 44-50). L'Italien *et al.* teach that these formulations maintain stability upon storage under refrigerated or room temperature conditions (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Keene, Skrabanja and L'Italien to make the instant invention of a pharmaceutical acceptable solution formulation suitable for multi-use comprising human FSH and phenol. The motivation and expected success is provided by Keene, Skrabanja and L'Italien. The expression of biologically active recombinant human FSH (Keene *et al.*) avoids the need of purifying FSH from natural sources. The cartridge of Skrabanja *et al.* provides the convenience of stable multiple uses of FSH pharmaceutical formulations. L'Italien *et al.* teach that pharmaceutical formulations comprising anti-microbial preservatives such as phenol help maintain the stability upon storage under refrigerated or room temperature conditions.

Therefore, the scientific reasoning and evidence as a whole indicates that the rejection under 35 U.S.C. 103(a) should be maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 161-163 are directed to an invention not patentably distinct from claims 1-8 of commonly assigned U.S. Patent 6,573,237 B2, for the reasons set forth below.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent 6,573,237 B2, discussed below, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Claims 161-163 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,573,237 B2 in view of Keene *et al.*, The Journal of Biological Chemistry Vol. 264/9: 4769-4775 (1989) and Skrabanja *et al.*, EP 0853 945 A1.

The instant claims are drawn to a pharmaceutically acceptable solution formulation comprising human FSH (concentrations 5.0ug/ml to 2mg/ml) and a preservative in a aqueous diluent, wherein the preservative is selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol and mixtures thereof, wherein the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6, held together by noncovalent interactions and wherein the formulation is suitable for multi-dose administration by injection.

The claims 1-8 of U.S. Patent No. 6,573,237 B2 are drawn to a soluble formulation comprising nicotinamide, a hydrophobic preservative, a medically useful peptide or protein selected from the group consisting of FSH and FSH variants. The preservative of the soluble formulations include phenol and m-cresol. Although the conflicting claims are not identical, they are not patentably distinct from each other because U.S. Patent No. 6,573,237 B2 teach a formulation comprising FSH and FSH variants as the medically useful peptide and preservatives such as phenol or m-cresol.

Thus, the claims of U.S. Patent No. 6,573,237 B2 teach a formulation comprising FSH and phenol or m-cresol. The claims of U.S. Patent No. 6,573,237 B2 does not recite that the formulation is suitable for multi-dose administration by injection or the SEQ ID NOs of the α-subunit and β-subunit of FSH.

Keene *et al.* teach the expression of biologically active recombinant human FSH (α-subunit is SEQ ID NO:5 and β-subunit is SEQ ID NO:6).

Skrabanja *et al.* teach concentrations of FSH which overlap the concentrations in the instant claims (page 5, lines 5-14). Skrabanja *et al.* teach an article of manufacture comprising a vial or a pen-injector device. The formulation of FSH can be in the form of a cartridge for multiple uses (page 5, lines 21-45).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of U.S. Patent No. 6,573,237 B2 to make the instant invention of a pharmaceutical acceptable solution formulation suitable for multi-use comprising FSH (α-subunit having SEQ ID NO:5 and β-subunit having SEQ ID NO:6) and phenol or m-cresol. The motivation and expected success is provided by Keene and Skrabanja. The expression of biologically active recombinant human FSH (of Keene *et al.*) avoids the need of purifying FSH from natural sources. The cartridge of Skrabanja *et al.* provides the convenience of stable multiple uses of FSH pharmaceutical formulations.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
9/14/04

Elizabeth C. Kennonen